

# Role of inflammatory cytokines in distant metastasis of non-small cell lung cancer

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## BACKGROUND

Inflammation is an essential component of the tumor microenvironment. Cytokines involved in inflammation can also promote the formation of premetastatic niches and distant metastases (according to D. Layden's theory).

The aim of this study was to identify which cytokines are associated with the distant metastases in NSCLC.

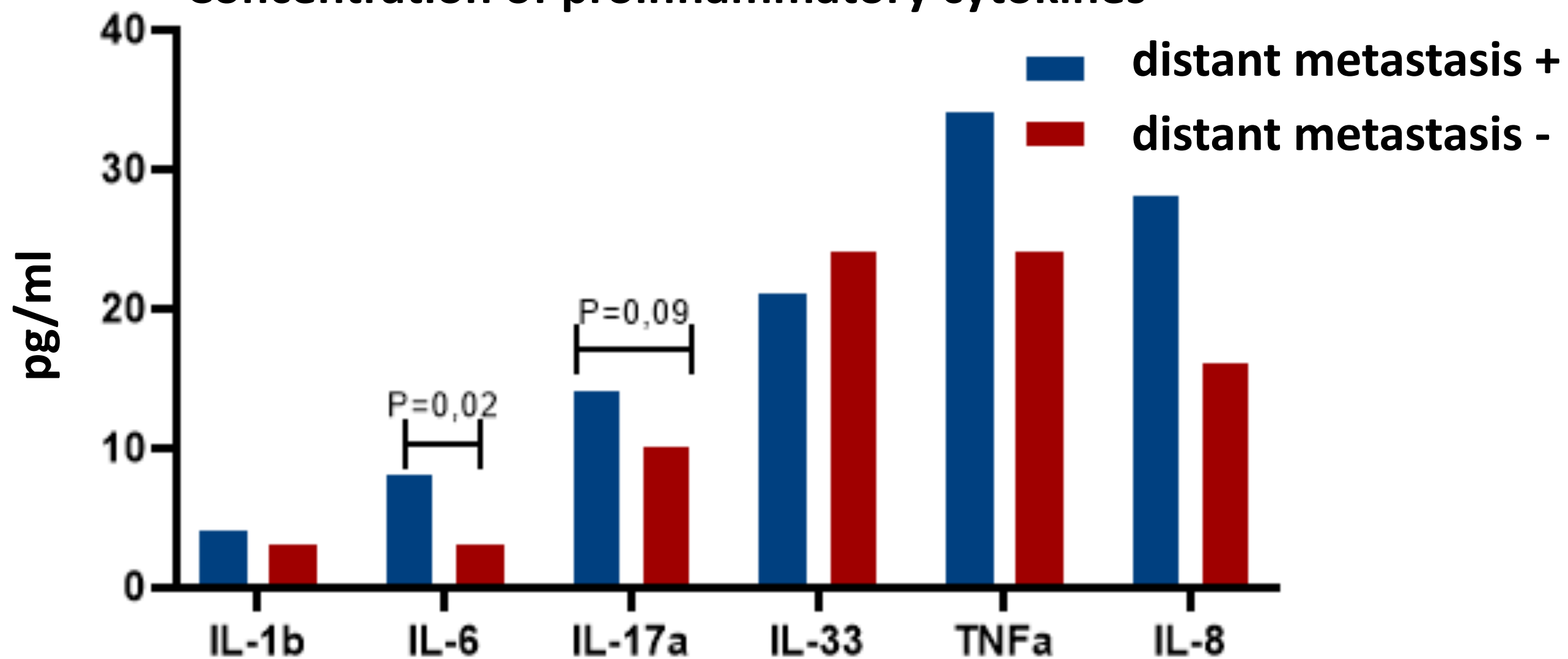
## METHODS:

The prospective study included 35 patients, male – 27 (77 %), female – 8 (23 %) with T1–4N0–2M0 non-small cell lung cancer (NSCLC) treated at Cancer Research Institute, Tomsk National Research Medical Center. Seventeen (49 %) of the 35 patients received 2–3 courses of neoadjuvant chemotherapy (NACT). The concentration of IL-1b, IL-2, IL-4, IL-6, IL-10, IL-12, IL-17a, IL-33, TNF $\alpha$ , IFN $\gamma$ , CXCL-8 (IL-8), CCL-2 (MCP-1), CCL-5 (RANTES), CXCL-12 (SDF-1) and VEGFA was determined in the serum by the Luminex xMAP technology (“Milliplex MAP Kit”, Merck Millipore, USA). All statistical analyses were performed in the GraphPad Prism version 8.3.0 (GraphPad Software, USA).

## FINDINGS

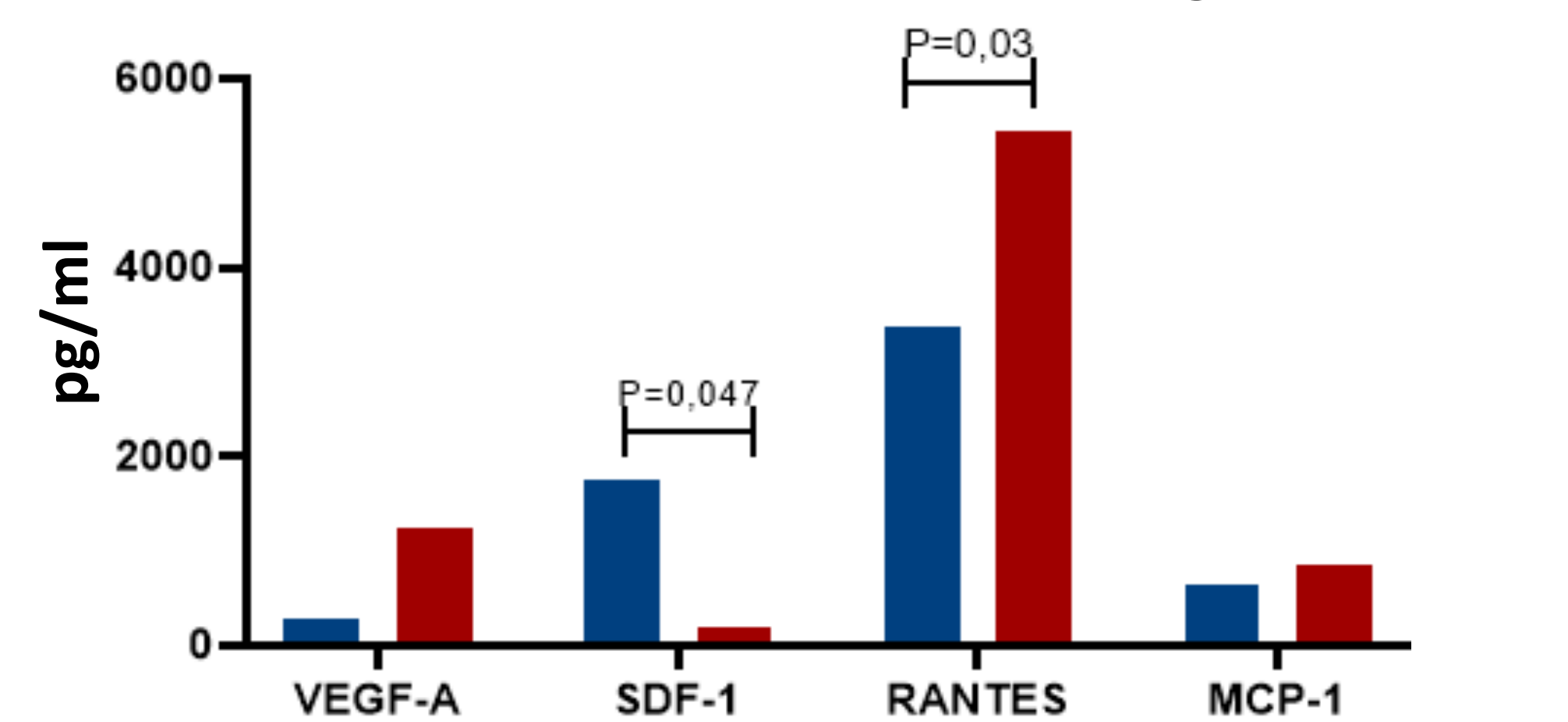
Logistic regression analysis made it possible to identify cytokines associated with the distant metastases. Thus, in patients who did not receive NACT, high concentrations of IL-6 and CXCL-12 (SDF-1) and the histological type of tumor (squamous cell carcinoma) were associated with a high risk of distant metastases ( $\chi^2 = 15.7$ ;  $p = 0.0013$ ). Model sensitivity – 100%, model specificity – 100%.

### Concentration of proinflammatory cytokines



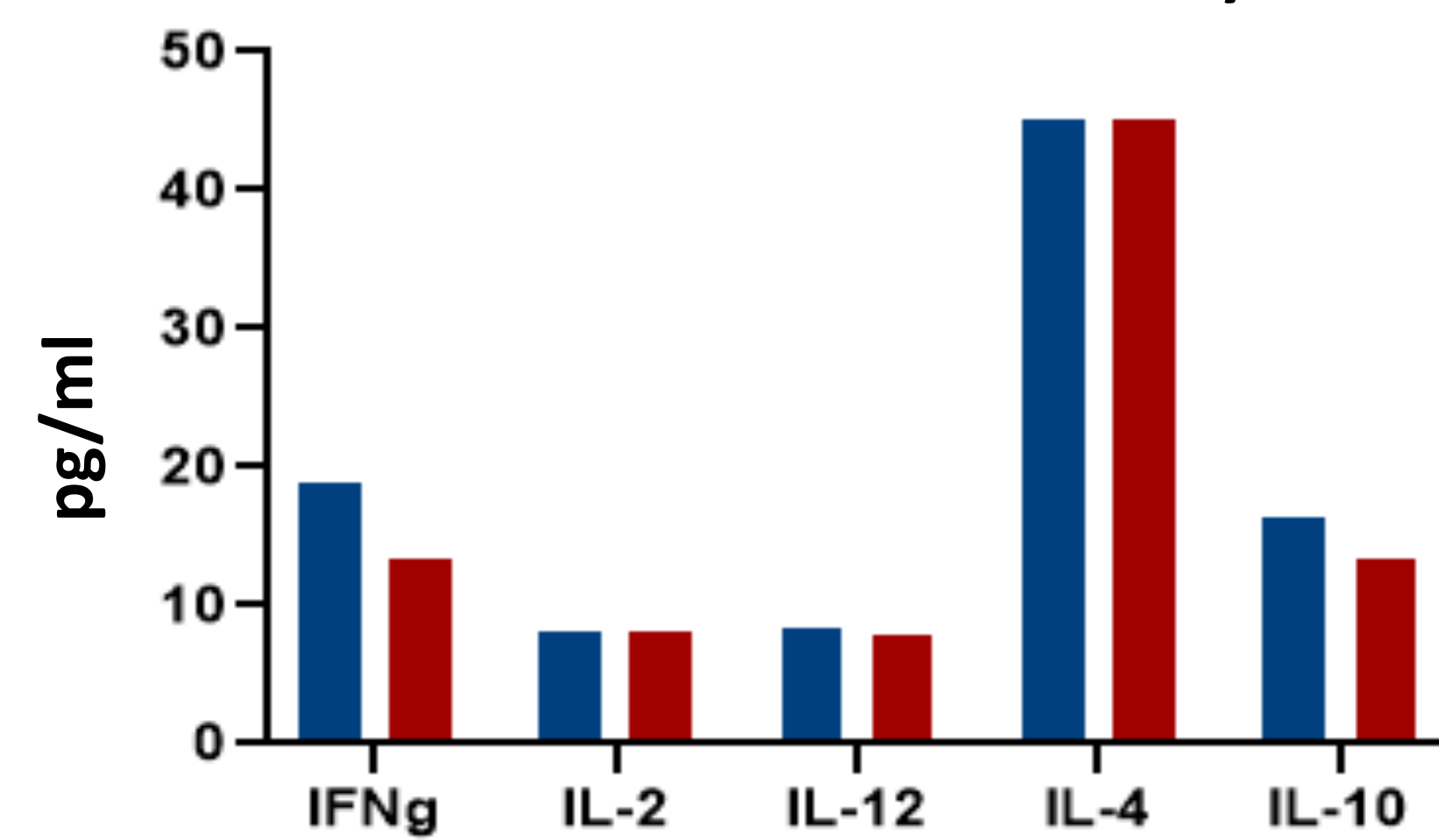
## FINDINGS

### Concentration of chemokines and growth factor

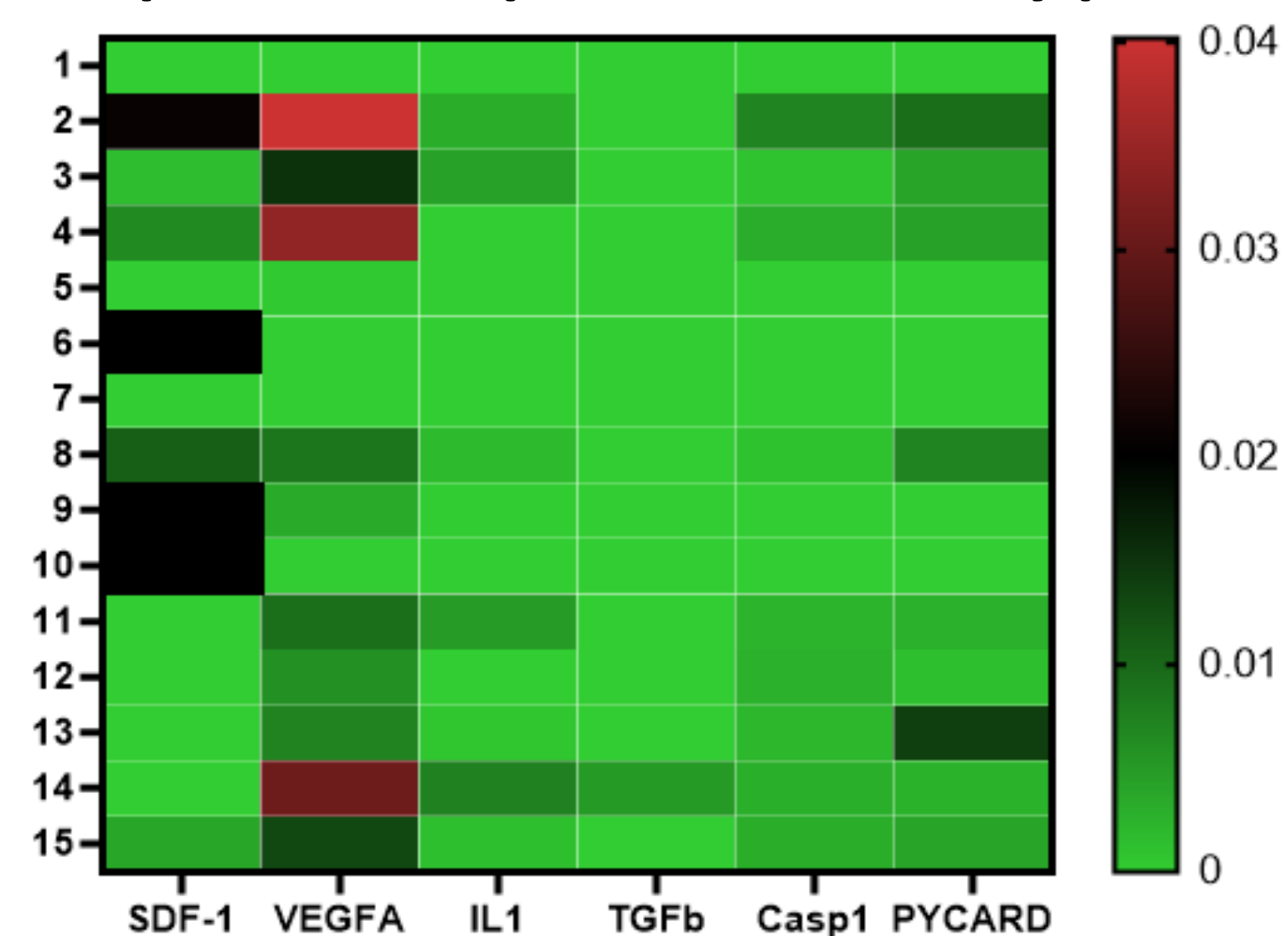


In patients after NACT a high concentration of IL-4 and a histological type of tumor (adenocarcinoma) were associated with a high risk of distant metastases ( $\chi^2 = 10.7$ ;  $p = 0.0047$ ). del sensitivity – 100%, model specificity – 100%

### Concentration of Th1 and Th2 cytokines

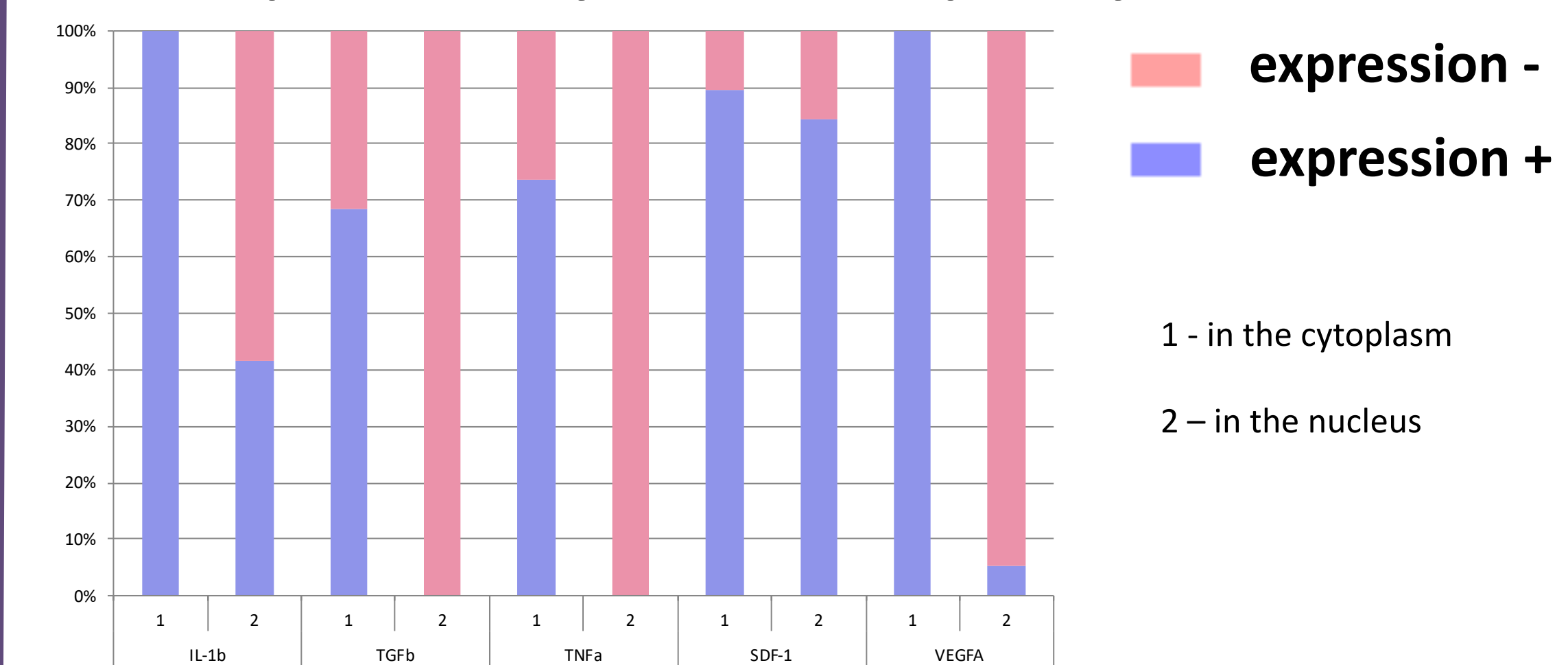


### Gene expression of pro-inflammatory proteins

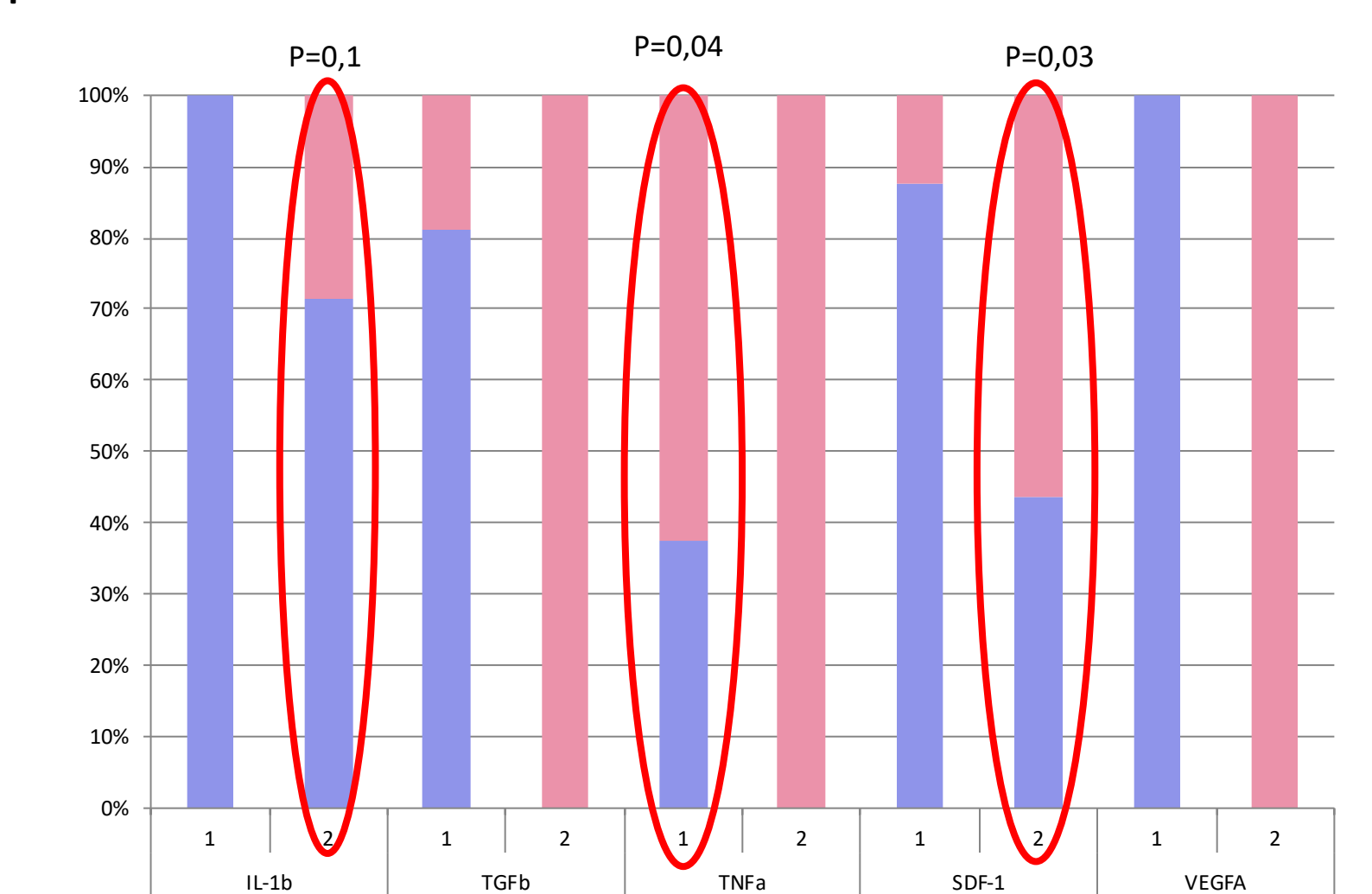


## FINDINGS

### Expression of cytokines in the primary tumor



### in patients without distant metastasis



### in patients with distant metastasis

Intracellular expression of IL-1, TNF $\alpha$  and SDF-1 changes in patients with distant metastases. These cytokines are involved in inflammation and the formation of the premetastatic niche.

## CONCLUSION

The concentration of serum cytokines involved in inflammation and the formation of the premetastatic niche varies in patients with NSCLC. A high risk of the distant metastases is associated with high concentrations of IL-6, CXCL-12 (SDF-1) and IL-4 and histological type of NSCLC. Also, it is necessary to remember that the NACT in some cases promotes the distant metastases.

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